IPSS «bother question» score predicts health-related quality of life better than total IPSS score

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Abstract

Objective

To investigate the role of bothersomeness of urinary symptoms on the general health-related quality of life (HRQoL) of patients with benign prostatic hyperplasia. We hypothesized that a higher International Prostate Symptom Score (IPSS) would be associated with a higher score on the IPSS bother question (IPSS-BQ), and a higher IPSS-BQ score would be the dominant factor associated with poorer general HRQoL.

Materials and methods

A case control, cross-sectional study design was used. Patients were selected according to strict inclusion and exclusion criteria and stratified by IPSS severity group (controls: IPSS < 8; moderately symptomatic: IPSS = 8-18; and severely symptomatic: IPSS > 18). The IPSS-BQ was used to analyse bothersomeness of urinary symptoms. A standardised, multidimensional measure of HRQoL (RAND-36) was used. Data were collected on prostate size, uroflowmetry parameters, prostate specific antigen and comorbidities that were quantified using the Charlson Index and the American Association of Anaesthesiologists (ASA) score. Multiple linear regression models were used to assess the impact of bothersomeness of urinary symptoms on physical and mental HRQoL. Cohen's d was used to determine the effect size.

Results

We included 83 patients in the statistical analysis. Linear regression analyses showed that the IPSS was not an independent predictor of HRQoL. Only the highest IPSS-BQ score was associated with both worse physical (P = 0.021) and mental (P = 0.011) HRQoL in the final model. The effect sizes were small to moderate.

34   *Conclusion*

35   The IPSS-BQ score is an important predictor of HRQoL. The IPSS-BQ score as a proxy should be regarded

36   as a standard outcome measure and reported in all LUTS-related research.

37

38   *Keywords: IPSS "bother question", RAND-36, Health-related quality of life, Bothersomness of LUTS*

39

40   Introduction

41   Benign prostatic hyperplasia (BPH) is a progressive disease and the main cause of lower urinary tract

42   symptoms (LUTS) in aging men[1]. The presence of moderate to severe LUTS is associated with

43   decrements in general health related quality of life (QoL)[2], which refers to "how health impacts on

44   an individual's ability to function and his or her perceived well-beeing in physical, mental and social

45   domains of life"[3] The degree to which these symptoms bother patients (bothersomeness) is a key

46   decision point in the diagnosis and treatment algorithm of the European Association of Urology 2020

47   Guidelines for non-neurogenic male-LUTS[4]. Most of the studies on BPH treatment have used

48   improvement in symptoms, as quantified by the International Prostate Symptom Score (IPSS), as

49   primary or secondary endpoints to evaluate efficacy[5-8]. However, the IPSS alone is not a strong

50   predictor of general health-related quality of life (HRQoL)[9]. Improved HRQoL should be the main

51   endpoint of any proposed treatment modality for BPH. Therefore, comprehending the level of

52   impairment in HRQoL due to LUTS for a unique patient should be valuable adjunct information in all

53   treatment-evaluation research[10]. The IPSS bother question (IPSS-BQ) is the most used measure of

54   disease-specific quality of life QoL in the evaluation of men with BPH[11]. Various studies have

55   demonstrated the reliability and validity of the IPSS-BQ and have reported a strong positive correlation

56   with other disease-specific QoL instruments with more items[12, 13]. However, to our best knowledge,

57   no published studies have investigated the role of the IPSS-BQ as a predictor of general HRQoL. The

58   most widely used questionnaire for assessing general HRQoL is the RAND 36. Although evaluations of

59   the general HRQoL of patients with LUTS using the standardised SF-36/RAND-36 questionnaire have

60   been published, these studies have only addressed the association between symptoms (IPSS= and

61   general HRQoL and not the association between bothersomness og LUTS (IPSS-BQ) and HRQoL [9, 14].

62   The aim of this study was to investigate the role of bothersomeness of urinary symptoms on the

63   general HRQoL of patients with LUTS, secondary to BPH. We hypothesised that a higher IPPS would be

64   associated with a higher IPSS-BQ, while a higher IPSS-BQ would be the dominant factor associated with

65   a poorer general HRQoL.

66

Material and Methods

Study design

A cross-sectional design was applied. The study was conducted in the Urologic Outpatient Clinic of Førde Central Hospital. The inclusion period was 20 November 2018 – 17 February 2021.

71

Participants

Patients were referred by their general practitioners (GPs) and selected by the first author if they met the study criteria (Table 1).

We did not impose limits on the inclusion criteria regarding prostate size, prostate specific antigen (PSA) value or maximum flow rate (Q-max) because we wanted our study population to be as representative as possible of the general population. Knowing that different categories of patients have different experiences of LUTS, we needed to have wide variation in our data in order to find weak correlations in our analysis of the link between patients' reports of bothersomeness of LUTS and perceived HRQoL. Reference data for HRQoL were derived for am representative survey of general population of Norwegian adults from 2015. The sample consisted of 947 males who completed the Norwegian version of the RAND-36.

Please see Table 1 for patient selection, workup and data collection.

84

Measurements

To assess symptom severity, we used the standard 7-item IPSS questionnaire. The eighth question of the IPSS, IPSS-BQ (i.e. 'If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?') was scored on a 6-point scale: 0 (delighted), 1 (pleased), 2 (mostly satisfied), 3 (mixed about equally satisfied and dissatisfied), 4 (mostly dissatisfied) and 5 (unhappy), with higher scores indicating worse QoL. Patients were initially divided in accordance with the scores of the standard IPSS groups: control group (0-7) moderately symptomatic group (8-19) and severely symptomatic group (20-35)[15].

The RAND-36 is a widely used HRQoL survey and a reliable tool for analysing group comparisons based on its internal consistency and test-retest reliability indexes[3, 16]. The instrument consists of 36 items that assess eight health concepts: physical functioning, physical role functioning, physical pain, general health, vitality, social functioning, emotional role functioning and mental health. The RAND-36 is not specific for any population or disease. Each subscale is converted to a 100-point scale, with 100 representing optimal HRQoL. The eight scales of the RAND-36 are calculated to yield overall physical and mental HRQoL summary scores[17].

100   The presence of comorbidities was assessed using the American Society of Anaesthesiology (ASA) score

101   and the Charlson Index[18].

102

103   *Sample size*

104   Given a power level of 80%, a two-tailed P-value of 0.05 and N = 83, a Pearson correlation of 0.3 is

105   likely to be statistically significant[19]. An effect-size of 0.3 indicates an thershold for effects that are

106   clinically relevant and potentially powerfull in bothe the short and the long run.[20]

107

108   *Statistical method*

109   To examine the associations between the different variables, we used analysis of variance (ANOVA) to

110   examine differences between the parameters of the three IPSS groups. Linear regression was used to

111   analyse the relationship between scores on the IPSS, IPSS-BQ and physical and mental domains of the

112   HRQoL based on the RAND-36. We used both an unadjusted and an adjusted model for age and

113   comorbidities as quantified by the ASA score and the Charlson Index. We then stratified the patients

114   according to the degree to which their symptoms were bothersome, as assessed using the IPSS-BQ.

115   Comparisons were analysed between the IPSS severity groups, the IPSS-BQ and an age-matched

116   sample of males from the general population of Norway[16]. To assess differences between the

117   groups, we used Cohen's d effect size calculation model, where a 0.2 difference in the standard

118   deviation is considered a small difference, 0.5 is a medium difference and 0.8 is a large difference[21].

119   We reported two-tailed P-values and 95% confidence intervals. The IBM SPSS Statistics Version 26

120   software was used for the statistical analyses.

121

Results

123   Among the 169 patients that met the study's criteria, 91 (53%) signed forms indicating their informed

124   consent to participate in the study. Eight patients were excluded (5 with a prostate cancer diagnosis;

125   1 with an acute leukaemia diagnosis; 1 with a bladder cancer diagnosis; and 1 who withdrew informed

126   consent, all of them within one month of the inclusion date). Thus, 83 patients were considered for

127   the statistical analysis. The general characteristics of the patients are summarised in Table 2. The

128   cohort is typical of patients referred to urologists for LUTS examinations. The control group represents

129   an average representation of typical men between 50 and 80 years of age in Norway. Initial analysis of

130   the IPSS-BQ as an independent predictor of HRQoL revealed that a decrease in mental HRQoL with an

131   increase in bothersomeness of urinary symptoms was not a linear function, but there was a clear

132   reduction in mental HRQoL from the IPSS-BQ score of 2, to an IPSS-BQ score of 3. This reduction was

133 present but not obvious for physical HRQoL on the RAND-36. Consequently, we divided the patients in

134 two groups: IPSS-BQ = 0-2, n = 35 and IPSS-BQ = 3-5, n = 48 (see Supplementary Tables for details).

135 The results of the linear regression showed that the IPSS is a strong predictor of the IPSS-BQ in an

136 unadjusted model and that the association was preserved when adjusting for age and comorbidity.

137 However, when the regression model was used to assess the impact of the IPSS on mental and physical

138 HRQoL, the IPSS score had no significant effect on either of these two parameters. When the IPSS-BQ

139 was added to the model, significant effects on the mental and physical HRQoL scores were observed.

140 The details are summarised in Table 3. Cohen's effect sizes for the physical (d = 0.5) and mental (d =

141 0.7) HRQoL domains were medium and large, respectively. The effect sizes of all the domains of the

142 RAND-36 are presented in the Supplementary Tables.

143 We then compared the study population with Norwegian normed data. The age-adjusted mental

144 HRQoL of the Norwegian population was 81.3 (SD = 15.9), and the physical HRQoL was 76.6 (SD = 20.8).

145 When the study population was stratified by IPSS group there were only small differences, as evaluated

146 using Cohen's d, in mental and physical HRQoL between the three study groups and the normed data.

147 However, there were medium size differences in the vitality domain. The details are illustrated in

148 Figure 1A. When the study population was stratified by IPSS-BQ group, moderate differences were

149 found in mental and physical HRQoL compared to the normed data, and again, a medium size effect

150 was found in the vitality domain (Figure 1B).

151

Discussion

153 We explored the role of bothersomeness of urinary symptoms and its relationship with HRQoL and

154 urinary symptom status. The degree to which symptoms become bothersome or worrisome to a

155 patient usually provides the basis for his decision to seek medical treatment. Numerous studies have

156 shown that the "bother question" provides a reproducible valid tool for evaluating changes in the

157 status of LUTS[13, 22, 23]. We have developed a model showing that the objective quantification of

158 symptoms (using the IPSS) may influence the assessment of bothersomeness of urinary symptoms

159 (IPSS-BQ), which in turn, may influence the HRQoL of patients (RAND-36). The IPSS alone showed no

160 significant associations with patients' HRQoL. The IPSS-BQ was the only variable that correlated with

161 patients' mental and physical HRQoL. As the primary goal of LUTS treatment is an improvement in

162 HRQoL, evaluations of new treatment methods based only on an improved IPSS are probably

163 insufficient to conclude that these treatments cause consequent improvement in HRQoL.

164 Although numerous articles have been published on the bother question's association with LUTS, none

165 has addressed the relationship between that the degree to which it is bothersome to the patient and

166 general HRQoL.

167   Salinas-Sanches (2001) investigated the HRQoL of patients on the waiting list for BPH surgery using the

168   SF-36, and found they had a poorer HRQoL than the general population of the same age. A major

169   limitation of this study is bias in the selection of patients with indications for surgical treatment. Thus,

170   it could be expected that these patients would be likely to have poorer HRQoL. However, this study is

171   one of the first studies that objectively quantified the HRQoL of the study group using a validated tool

172   (SF-36) and compared the results with normed data from an age-matched national population[14].

173   Welch (2002) conducted a large survey of United States (US) men participating in the Health

174   Professionals Follow-Up Study. Although they did not use the two composite scores that we used their

175   findings are similar to ours. The patients with severe LUTS had small to moderate differences from the

176   age-matched sample from the general population of the US with regard to vitality/energy and the

177   ability to work and perform daily tasks because of their illness. These findings were consistent when

178   they were adjusted for confounding factors, such as comorbidities However, they did not specifically

179   address the relationship among the scores on the IPSS, IPSS-BQ and SF-36[9].

180   One possible explanation for our findings is that symptoms, per se, have different meanings for

181   different patients. It is only when the subjective experience of these symptoms becomes bothersome

182   that there is a consequent reduction in HRQoL. This is the main driver for patients to seek medical

183   attention. It is improvement in their HRQoL and resolution of their bothersome urinary symptoms that

184   patients expect from the treatment. Neither improved symptom scores nor urinary flow rate are

185   parameters that are directly acknowledged by the patients.

186   The strengths of this study include its strict inclusion and exclusion criteria that narrowed down

187   patients' signs and symptoms to BPH as the most probable aetiology of LUTS; the inclusion of a control

188   group; the homogeneity of the groups that allowed for good comparisons; the use of only one

189   investigator to perform transrectal prostate measurements, thereby eliminating observer bias; and the

190   completeness of the data and comparisons of HRQoL between the patients and the age-matched

191   sample from the general population of Norway. The limitations of the study include its cross-sectional

192   design and small sample of patients that were previously referred to a urologist by a GP. This study

193   population mainly included urology patients and might not reflect an accurate picture of patients in

194   the general population. Another drawback is the use of the IPSS because it does not assess the

195   incontinence aspects of LUTS, which are known to be extremely bothersome[24].

196   Last, as this is a cross-sectional study, it provides only a static picture of IPSS-BQ as a parameter for

197   HRQoL.

198

Conclusion

The IPSS-BQ is a better predictor of HRQoL than the total IPSS. The IPSS-BQ as a proxy for HRQoL should be regarded as the standard outcome measure and reported in all LUTS-related research. Further longitudinal studies are needed to examine the reliability of this parameter as an instrument for assessing changes over time and responses to treatment.

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Author contributions

FHN: Project/Protocol development, Data collection and management, Data analysis, Manuscript writing/editing.

JRA: Project/Protocol development, Data management, Data analysis, Manuscript writing/editing, Supervision

CB: Project/Protocol development, Data analysis, Manuscript writing/editing, Supervision.

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212

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Compliance with ethical standards

217

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290

Table 1. Patient Selection, Workup and Collected Data

Inclusion Criteria
- Male age between 50 and 80 years   - Willingness to sign the informed consent form   - IIEF-5 score >5   - ECOG performance status 0-1

Exclusion Criteria
- Unwilling to sign the informed consent form   - Drug treatment for LUTS or sexual dysfunction   - Any additional drug treatment with a known effect on BPH symptoms (diuretics, antihistamines, calcium channel blockers, phytotherapy or tricyclic antidepressants) for any length of time in the four weeks prior to inclusion   - Presence of other urinary disorders – chronic pelvic pain, urethral strictures, bladder cancer, previous TUR-P or laser procedure, pelvic radiation or surgery, urinary tract infection   - Any known cancer diagnosis except non-malignant melanoma of the skin within the last 5 years   - Severe cardiac comorbidities – ASA score >3   - Presence of neurodegenerative disorders (i.e. Parkinson's disease, Alzheimer's disease, etc.)   - Unwilling to report sexual function   - Penile conditions that prevent sexual act (i.e. penis cancer)   - ECOG performance status > 1

Workup and Collected data

- Blood samples
- Questionnaires:
  - IPSS
  - IIEF
  - RAND-36
- Medical history
  - ASA
  - Charlson index
- Demographic data

→

- Uroflowmetry
- Post-void residual urine (scanner)
- Digital rectal examination
- Transrectal ultrasound of the prostate
  - Volume
  - Abnormalities

→

Discretionary tests (if indicated)
- Cystoscopy
- Imaging of upper urinary tract
- Bladder diary
- Urodynamic testing

Treatment according to the clinical situation

Note: ASA = American Society of Anaesthesiologists; ECOG = Eastern Cooperative Oncology Group; LUTS = lower urinary tract symptoms; TUR-P = Transurethral resection of the prostate; BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score; IIEF-5 = International Index of Erectile Function 5-item version; RAND-36 = RAND 36-Item Health Survey

Table 2. Patients' Characteristics

Variables	Control Group (IPSS <8) n = 20 Mean (SD)*	Moderately Symptomatic (IPSS 8-18) n = 35 Mean (SD) *	Severely Symptomatic (IPSS>18) n = 28 Mean (SD) *	P-value
Age (years)	63.4 (7.1)	65.2 (5.9)	63.4 (6.8)	0.458
IPSS-BQ	1.1 (0.9)	2.7 (1.1)	3.6 (0.9)	**<0.001**
ASA Classification	1: 14 (70%) 2: 5 (25%) 3: 1 (5%)	1: 11 (31.4%) 2: 21 (60%) 3: 3 (8.6%)	1: 10 (35.7%) 2: 18 (64.3%)	**0.031**
Charlson Index	0: 13 (65%) 1: 6 (30%) 2: 1 (5%)	0: 23 (65.7%) 1: 7 (20%) 2: 5 (14.3%)	0: 20 (71.4%) 1: 6 (21.4%) 2: 2 (7.1%)	0.742
Prostate Volume (cm^3)	56.7 (28.4)	53.9 (23.4)	50.0 (21.9)	0.629
Residual Urine (ml)	81.6 (36.2)	95.5 (122.3)	121.8 (144.7)	0.614
Q-max (ml/sec)	21.3 (11.4)	16.8 (10.3)	14.0 (7.3)	0.134
PSA (µg/L)	3.5 (3.4)	3.1 (3)	3.2 (3.2)	0.877
Body Mass Index (kg/m^2)	26.9 (3.2)	27.5 (4.4)	26.9 (3.6)	0.768
Rand 36 domains				
Physical Function	92.0 (13.2)	91.6 (8.1)	88.0 (18.4)	0.503
Role Physical	83.8 (32.7)	79.3 (32.4)	74.1 (38.8)	0.632
Bodily Pain	73.6 (21.8)	66.6 (20.3)	70.8 (27.4)	0.534
General Health	75.8 (17.9)	67.1 (16.1)	67.3 (20.7)	0.195
Vitality	74.0 (19.2)	69.6 (14.5)	58.8 (20.1)	**0.009**
Social Function	88.8 (15.7)	87.1 (16.7)	84.4 (21.7)	0.699
Role Emotional	91.7 (26.2)	86.7 (28.2)	85.7 (32)	0.763
Mental Health	86.2 (13.8)	84.2 (10)	82.7 (12)	0.597
Physical HRQoL	81.3 (18.6)	76.1 (15.3)	75.1 (23.4)	0.511
Mental HRQoL	85.2 (16.7)	81.9 (14.5)	77.9 (16.5)	0.282

Note: P-values are for the ANOVA results; *The ASA Classification, Charlson Index,reports the number of patients in each category not mean and standard deviation; IPSS-BQ = Bothersomeness of urinary symptoms as reported in question 8 of the IPSS; IIEF = International Index of Erectile Function; Q-Max = peak urinary flow ; HRQoL = health related quality of life .

Table 3. Linear Regression Models

Variables	Unadjusted			Adjusted		
	B (95% CI)	Beta	P-value	B (95% CI)	Beta	P-value
Model 1: IPSS-BQ (IV)						
IPSS	0.13 (0.10 – 0.15)	0.72	**<0.001**	0.13 (0.10 – 0.15)	0.73	**<0.001**
Age	-0.03 (-0.08 – 0.02)	-0.14	0.196	-0.03 (-0-07 – 0.00)	-0.16	0.060
Charlson Index	0.06 (-0.39 – 0.52)	0.03	0.778	0.13 (-0.24 – 0.50)	0.06	0.496
ASA	0.16 (-0.36 – 0.68)	0.07	0.550	0.00 (-0.46 – 0.46)	0.00	0.991
Model 2: Physical HRQoL (IV)						
IPSS	-0.24 (-078 – 0.29)	-0.10	0.369	0.40 (-0.33 – 1.13)	0.17	0.275
IPSS-BQ	-10.22 (-18.40 – -2.03)	-0.27	**0.015**	-13.61 (-25.07 – -2.15)	-0.35	**0.021**
Age	0.24 (-0.40 – 0.89)	0.08	0.458	0.28 (-0.41 – 0.98)	0.10	0.418
Charlson Index	-4.02 (-10.30 – 2.26)	-0.14	0.206	-0.52 (-7.84 – 6.80)	-0.02	0.888
ASA	-5.88 (-13.05 – 1.30)	-0.18	0.107	-6.88 (-15.88 – 2.12)	-0.21	0.132
Model 3: Mental HRQoL (IV)						
IPSS	-0.40 (-0.83 – 0.04)	-0.20	0.075	0.19 (-0.41 – 0.78)	0.09	0.537
IPSS-BQ	-10.64 (-17.26 – -4.03)	-0.34	**0.002**	-12.27 (-21.66 – -2.88)	-0.39	**0.011**
Age	0.06 (-0.48 – 0.60)	0.03	0.821	0.08(-0.49 – 0.64)	0.03	0.792
Charlson Index	-1.71 (-6.94 – 3.53)	-0.07	0.518	1.01 (-4.98 – 7.01)	0.04	0.737
ASA	-4.59 (-10.54 – 1.36)	-0.17	0.129	-5.37 (-12.74 – (2.00)	-0.20	0.151

Note: IPSS-BQ = Bothersome urinary symptoms, as assessed using question 8 of the IPSS; IV = independent variable. Age and IPSS were treated as continuous independent variables and IPSS-BQ was treated as a binary variable (score ≤ 2 = 0 and > 2 = 1).

The variance explained by the adjusted models are as follows: Model 1 = 52.7%, Model 2 = 6.9% and Model 3 = 8.7%.

Figure 1. Cohen's d effect sizes for the three IPSS groups vs the Norwegian normed data

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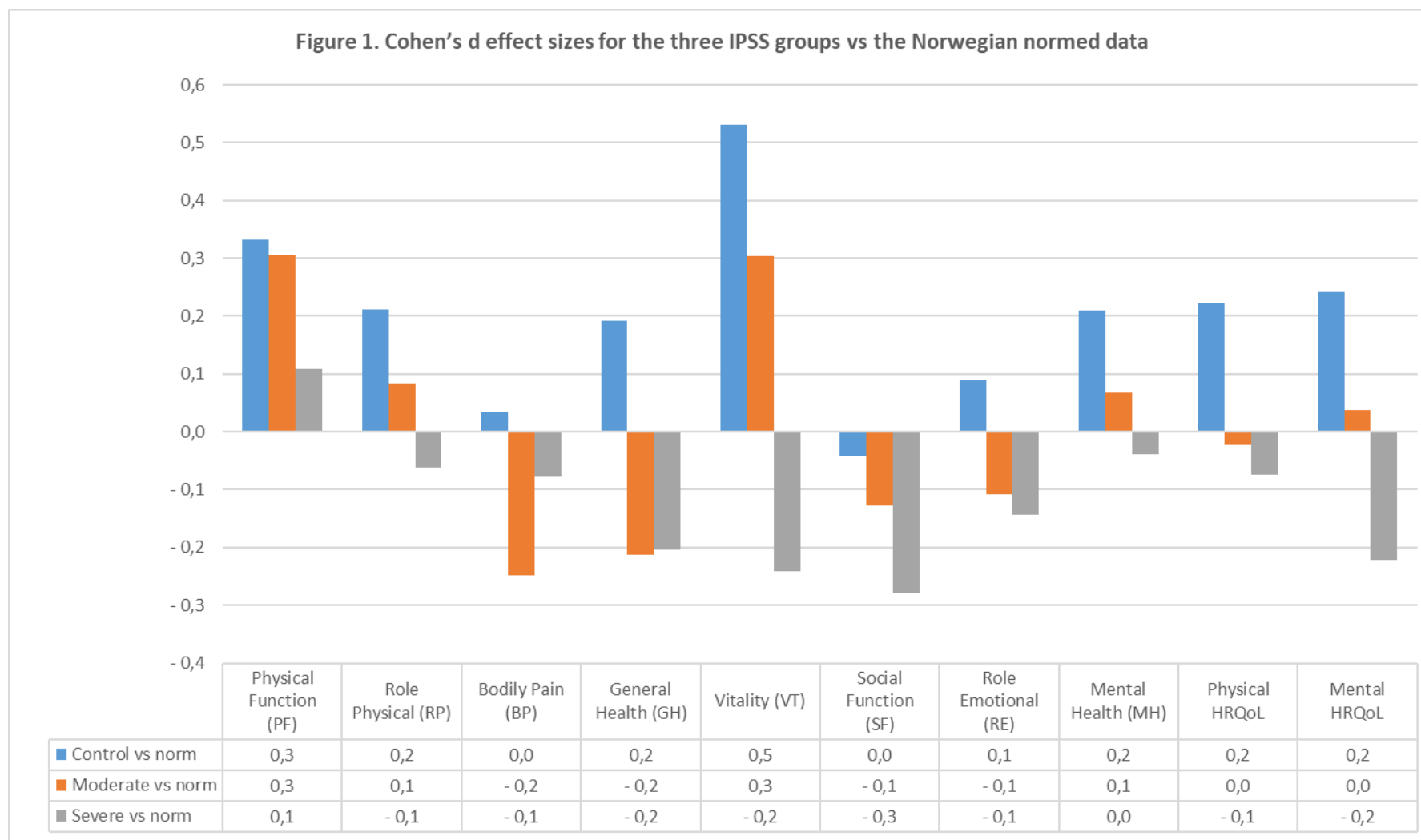|	Physical Function (PF)	Role Physical (RP)	Bodily Pain (BP)	General Health (GH)	Vitality (VT)	Social Function (SF)	Role Emotional (RE)	Mental Health (MH)	Physical HRQoL	Mental HRQoL
Control vs norm	0,3	0,2	0,0	0,2	0,5	0,0	0,1	0,2	0,2	0,2
Moderate vs norm	0,3	0,1	- 0,2	- 0,2	0,3	- 0,1	- 0,1	0,1	0,0	0,0
Severe vs norm	0,1	- 0,1	- 0,1	- 0,2	- 0,2	- 0,3	- 0,1	0,0	- 0,1	- 0,2

Figure 2. Cohen's d effect sizes for the two IPSS-BQ groups vs the Norwegian normed data

Figure 2. Cohen's d effect sizes for the two IPSS-BQ groups vs the Norwegian normed data

	Physical Function (PF)	Role Physical (RP)	Bodily Pain (BP)	General Health (GH)	Vitality (VT)	Social Function (SF)	Role Emotional (RE)	Mental Health (MH)	Physical HRQoL	Mental HRQoL
IPSS-BQ≤2 vs norm	0,4	0,3	0,1	0,2	0,6	0,1	0,3	0,3	0,3	0,4
IPSS-BQ>2 vs norm	0,1	-0,1	-0,3	-0,3	-0,1	-0,4	-0,3	-0,1	-0,2	-0,3